The Role of MRI in Screening Women at High Risk for Breast Cancer

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Genetic predisposition accounts for an estimated 5 to 10% of all breast cancers and leads to a minimum of 10,000 new breast cancer cases diagnosed in the U.S. each year. Approximately half of all genetically induced breast cancer cases are thought to be due to a mutation in the BRCA1 or BRCA2 gene, the other half by as yet unidentified gene mutations. Carriers of genetic mutations have approximately a 70% (for BRCA2) to 85% (for BRCA1) lifetime risk of developing breast cancer [1,2]. For patients who are not known to have a genetic mutation, models have been developed which can estimate a woman's lifetime risk for developing breast cancer. These models, which have been validated by independent researchers, can indicate which women are at significantly high risk for breast cancer, even in the absence of a known genetic mutation within the family.

Women with a personal history of breast cancer are also at increased risk. These women have a 2 to 6 fold increased risk of developing breast cancer in the contralateral breast than women in the general population have of developing a first breast cancer [3-5]. In addition, women with a history of therapeutic chest radiation have a significantly increased risk of developing breast cancer. Breast cancers have been reported at high rates in women treated with radiation for Hodgkin's disease as early as 10 years after treatment [6].

Until recently, mammography was the only recommended imaging modality used to detect clinically occult breast cancer. Although mammography is the current standard screening study for breast cancer, it has difficulty in demonstrating cancer in radiographically dense breasts. Women at high risk tend to develop cancer at a younger age. By age 50 it is estimated that more than 50% of BRCA1 and BRCA2 mutation carriers have already developed the disease [7]. Breast cancer in women with a history of chest wall irradiation tends to occur between ages 30 and 40.

The challenge of screening young women at high risk with mammography has stimulated exploration of alternative or adjunctive imaging techniques, including magnetic resonance imaging (MRI). Until recently, there were sparse data on the sensitivity and specificity of MRI in screening high risk women. Thus it was challenging to determine whether or not the sensitivity and specificity of the exam were acceptable and whether the benefits of screening MRI were likely to exceed the harms. Over the past decade, results from 8 trials from Germany, Canada, Italy, the Netherlands, the United Kingdom and the United States have been published.[8-15] The results of these 8 trials are summarized in Table 1.

The 3 largest prospective studies to date are from the Netherlands, England, and a trial by the International Breast MRI Consortium including sites from the United States, Canada and Germany.[13, 15, 14] The sensitivity of MRI reported in these 3 trials was consistently higher than that for mammography,

with MRI sensitivities ranging from 71-100% compared to sensitivities of mammography in the same population ranging from 25-40%. The specificities were also acceptable, ranging from 81% to 93%.

Kuhl [8] published the first study comparing the three imaging modalities in high risk women. 192 asymptomatic high-risk women underwent screening with mammography, ultrasound (US) and MRI. Nine women were diagnosed with breast cancer. The cancer yields during the first two years of the study of mammography, US and MRI were 3/192 (1.5%), 3/192(1.5%) and 9/192(4.7%) respectively. Six of the nine cancers were identified in the first round of screening, 3 cancers were identified in 101 women in the second round of screening. The sensitivities of mammography, US and MRI were 33%, 33%, and 100% respectively. The sensitivity of mammography and ultrasound combined was 44%. The specificities were 93%, 80% and 95% respectively.

In a separate study [9], 236 asymptomatic high risk women underwent screening with mammography, US and MRI. Sixteen invasive and six non-invasive cancers were diagnosed. The cancer yields of mammography, US and MRI were 8/236 (3.4%), 7/235 (3%) and 17/236 (7.2%) respectively. The sensitivities of mammography, US and MRI in detecting invasive cancer were 36%, 33%, and 77% respectively. The specificities were 99%, 96%, and 95% respectively.

In a study from the Netherlands by Tilanus-Linthorst et al, women at high risk of breast cancer benefited from intensive screening by having their cancers detected at an earlier stage compared to women who do not participate in screening programs [16]. In this study, women who did not participate in screening programs were significantly less likely to have early T1N0 cancers compared to women under surveillance (46% vs. 81%). These women outside of the screening program carried over two-fold the risk of node positive disease compared to their cohorts in a screening program (42% vs. 19%). These investigators also found that MRI screening of high-risk populations detected tumors occult at physical exam and on mammography. In a subgroup of patients screened with MRI, 3 of 11 cancers were identified on MRI only.

The largest published study to date reported on screening performance in 1909 women at increased risk in the Netherlands [13]. Fifty-one cancers were diagnosed. The sensitivity of clinical breast examination, mammography and MRI in this study were 17.9%, 33% and 79.5% respectively. The overall accuracy of MRI was significantly better ($P<0.05$) compared to mammography. The two external age-matched control groups had more than double the incidence of positive nodes and micrometastases than the women in the MRI surveillance group ($P<0.001$).

Because of preliminary but consistent published reports from multiple investigators in the United States, Canada and Europe supporting the added benefit of MRI and US in detecting cancer in women at high risk, the American Cancer Society currently recommends that women discuss with their clinicians the potential benefits and risks of adding alternative screening methods such as ultrasound or MRI to complement their mammographic screening [17]. In 2003, after thorough review of the published literature, several third party payers

agreed to reimburse for screening MRIs in women at high risk for breast cancer [18].

There are potential harms associated with screening MRI. Specificity of MRI tends to be lower than for mammography and variable across published studies. In the study of 1909 women in the Netherlands, the specificity of clinical breast examination, mammography and MRI were 98.1%, 95.0% and 89.8% respectively, and the authors note that screening with MRI led to twice as many unneeded additional examinations as did mammography (420 vs. 207) and three times as many unneeded biopsies (24 vs. 7) [13]. MRI has not been studied in the general population as a screening tool, and the results from MRI screening of high-risk women may not apply to women at average risk. The high cost of MRI (approximately ten times higher than mammography) and its relatively low specificity (compared to mammography) probably prohibit its routine use for screening general populations. Also, MRI is time-consuming, requires intravenous contrast administration, and may be problematic for claustrophobic patients.

In summary, there is a population of women at high risk for developing breast cancer for whom we do not have clear recommendations for care. Consistent results from multiple studies demonstrate MRI can detect cancers that are occult on both clinical exam and mammography. Recommendations for screening MRI of high risk women must be based on carefully collected data with analyses of cancer detection rates, biopsy rates and costs. Until more definitive information is available, enthusiasm for this exciting breast imaging tool must be tempered with careful and responsible application.

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Table 1. Comparative Sensitivity of Screening Mammography, Ultrasound (US), and Magnetic Resonance Imaging (MRI) in women at increased risk for breast cancer.

Author, Site (reference)	Study Design *	Follow-up (in months)	Mean Age in years (Range)	# Cancers detected/ Total # Screened	Sensitivity (%)			Cancer Yield from MRI alone (%) [Confidence Interval]**	Biopsies Recommended as a result of MRI (%)	PPV of Biopsies performed based on MRI
					Mammography	MRI	US			
Kuhl, Germany [8]	P	12	39 (18-65)	4.7% (9/192)	33% (3/9)	100% (9/9)	33% (3/9)	6/192 (3.1%) [0.9%, 6.0%]	14/192 (7.3%)	64%
Warner, Canada [9]	P	36	47 (26-65)	9.3% (22/236)	36% (8/22)	77% (17/22)	33% (7/21)	7/236 (3.0%)‡ [1.7%,7.1%]	37/236 (15.7%)	46%
Italian Multi-Center Project, Italy [10]	P	24	46 (25-77)	7.6% (8/105)	13% (1/8)	100% (8/8)	13% (1/8)	7/105 (6.7%) [2.7%, 13.3%]	9/105 (8.6%)	89%
Tilanus-Linthorst, Netherlands [11]	P	12	42 (22-68)	2.8% (3/109)	0%	100% (3/3)	---	3/109 (2.8%) [0.6%, 7.8%]	5/109 (4.6%)	60%
Morris, USA [12]	R	None	50† (23-82)	3.8% (14/367)	0%§	100% (14/14)	--	14/367 (3.8%) [2.1%, 6.3%]	59/367 (15.8%)	24%
MRI Screening Study Group, Netherlands [13]	P	33	40 (19-72)	2.4% (45/1909)	40% (18/45)	71% (32/45)	--	22/1909 (1.2%) [1.1%, 2.4%]	56/1909 (2.9%)	57%
IBMC, International [14]	P	None	45 (26-86)	1.1% (4/367)	25% (1/4)	100% (4/4)	--	3/367 (0.8%) [0.2%, 2.4%]	23/367 (6.3%)	17%
MARIBS, UK [15]	P	Varied 0 -72	40 (31-55)	5.1% (33/649)	40% (14/35)***	77% (27/35)	--	19/649 (2.9%) [1.7%-4.5%]	--	25%

* P=Prospective, R=Retrospective
† Reported Median
‡ One patient who had an MRI only cancer in this study did not receive ultrasound.
§ To be included in this study, subjects had to have a negative mammogram
*** Two cancers in the study were identified as 'interval' and not detected by either screening examination
** Exact binomial confidence interval